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Original article

Prevalence and predictors of high-on treatment platelet reactivity during prasugrel treatment in patients with acute coronary syndrome undergoing stent implantation



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ABSTRACT

Background: ADP-antagonists such as prasugrel have reduced but yet not overcome the phenomenon of high-on treatment platelet reactivity (HRPR), that has been shown to increase the rate of major cardiovascular events after an acute coronary syndrome (ACS) or percutaneous coronary intervention (PCI). However, the exact prevalence and the principal determinants of suboptimal platelet inhibition in patients treated with dual antiplatelet therapy (DAPT) with prasugrel have not been completely clarified and were therefore the aim of the present study.

Methods: We included patients (<75 years and >60 kg) treated with DAPT (aspirin + prasugrel) after PCI, mainly for an ACS. Platelet function test evaluation was performed at 1–3 months from discharge. HRPR was assessed by multiplate impedance aggregometry and defined for results above upper limit of normal after ADP stimulation.

Results: We included 190 post-ACS patients. HRPR with prasugrel was observed in 19 patients (10%). The prevalence of HRPR was stable in different high-risk subgroups of patients (female gender, hypercholesterolemic, and chronic kidney disease) whereas it was increased in diabetic patients ($p = 0.045$), with a significant interaction between diabetic status and HRPR ($p = 0.04$). However, at multivariate analysis, an impaired metabolic status, with higher levels of glycosylated hemoglobin and low-density lipoprotein (LDL) cholesterol, but not diabetic status, emerged as independent predictors of HRPR with prasugrel [OR (95% CI) = 2.1 (1.32–3.33), $p = 0.002$ and OR (95% CI) = 1.03 (1.01–1.05), $p = 0.003$, respectively], with a stronger linear relationship between ADP-mediated platelet aggregation and glycosylated hemoglobin levels ($r = 0.24$, $p = 0.002$), than for LDL-cholesterol ($r = 0.13$, $p = 0.09$).

Conclusions: In post-ACS patients treated with PCI and receiving DAPT with prasugrel, HRPR is observed in about 10% of patients. Impaired metabolic status, and especially elevated glycosylated hemoglobin, emerged as independent predictors of the suboptimal effectiveness of prasugrel.

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Introduction

Antithrombotic therapies represent a key point in the management of patients with acute coronary syndromes (ACS),

where the innovations in the pharmacological field and early aggressive strategies have led to a significant improvement in clinical outcomes [1–4].

Antiplatelet ADP-antagonists such as prasugrel, in particular, have demonstrated a reduction in major adverse ischemic events [5], overwhelming those complex metabolic interactions that contribute to the interindividual variability or a more delayed platelet inhibition with clopidogrel [6,7].

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However, recent studies have underlined the occurrence of a suboptimal platelet inhibition, or residual high-on treatment platelet reactivity (HRPR), even with newer antiplatelet drugs [8,9]. Indeed, inadequate platelet inhibition has been associated with a 2–9-fold increased risk of recurrent ischemic and thrombotic events, although it is still debated whether tailoring antiplatelet therapy could be more effective than a standard therapy in achieving a therapeutic window with dual antiplatelet therapy (DAPT) [10,11].

Variable rates (0–25%) of patients treated with prasugrel [12,13] have been reported to display HRPR, thus preventing the expected benefits of a more potent antiplatelet strategy, and especially in acute phase settings and in higher risk subsets of patients such as diabetics [14]. Nevertheless, in the absence of a standardized definition for HRPR assessment, the exact prevalence and clinical factors associated with an impaired response to prasugrel are still largely undefined, and were therefore the aim of the present study.

Methods

We included patients admitted to the Division of Cardiology, “Maggiore della Carità” Hospital, Eastern Piedmont University in Novara, Italy, from September 2013 to March 2016 and undergoing percutaneous coronary revascularization, mainly for an acute coronary syndrome. All patients receiving at discharge DAPT with aspirin (100–160 mg daily) and prasugrel (10 mg daily) were scheduled for chemistry and platelet function test evaluation at 1–3 months from discharge. The study was approved by our local Ethical Committee and informed consent was obtained by all patients.

Main demographic, clinical, and angiographic data, together with the indication for DAPT were recorded at discharge and included in a dedicated database, protected by password. Main cardiovascular risk factors were identified: hypertension was defined as systolic pressure >140 mmHg and/or diastolic pressure >90 mmHg or if the individual was taking antihypertensive medications. The diagnosis of diabetes was based on previous history of diabetes treated with or without drug therapies, fasting glucose >126 g/dl or HbA1c >6.5% at the moment of admission [15]. Compliance was assessed on the day of the scheduled platelet function test. Exclusion criteria were: patients' refusal or if the patient had given up prasugrel therapy, age ≥75 years, or body weight ≤60 kg.

Biochemistry analysis

Blood samples were drawn in the early morning, following a fasting period of 12 h. Glucose, creatinine, glycosylated hemoglobin, and lipid profile were determined as previously described [16]. Blood cell count was performed in a blood sample collected in tripotassium ethylenediaminetetraacetic acid (7.2 mg) tubes. These blood samples were analyzed within 2 h of venepuncture by automatic blood cells counter (A Sysmex XE-2100, Sysmex Europe GmbH).

Platelet aggregation

Platelet aggregation was determined by multiplate electrical impedance aggregometry (MEA) in the early morning (>12 h after last prasugrel dose). The aggregation tests were performed from 30 min to 2 h from blood collection [17]. Platelet aggregation was assessed after stimulation with arachidonic acid (0.5 mM) (ASPI test), collagen (3.2 µg/ml) (COL test), ADP (6.4 µM) with prostaglandin E1, and thrombin receptor activating peptide (TRAP-6; 30 µM). Results were expressed as arbitrary Aggregation Units (AU) and plotted against time recorded for 6 min, defining platelet

function as the area under curve (AUC). HRPR for prasugrel was defined for ADP test above 417 AUC (normal range: 417–1030) [18,19]. The test was repeated in patients with HRPR to confirm the finding.

Statistical analysis

All statistical analyses were performed by SPSS Statistics Software 22.0 (IBM SPSS Inc., Chicago, IL, USA). Continuous variables were represented as mean ± SD, while categorical variables as percentages. For non-normally distributed variables median and interquartile range [IQR] were reported. Patients were grouped according to the definition of HRPR. Chi-squared and ANOVA test were appropriately used to compare clinical and laboratory features between patients with and without HRPR. Non-parametric test for the comparison of medians was applied for non-normally distributed variables. Linear regression analysis was performed between platelet aggregation AUC and continuous variables associated with HRPR. Forward multiple logistic regression analysis was performed to evaluate independent predictors of HRPR, among the variables significantly associated with HRPR at univariate analysis (all variables with $p < 0.05$). Odds ratios for continuous variables were considered per unitary linear increase. A p -value <0.05 was considered statistically significant.

Results

Our population is represented by 190 patients undergoing coronary stenting, mainly post-ACS. The main demographic, clinical, and laboratory features of our population are listed in Table 1. HRPR with prasugrel was observed in 19 patients (10%). The test was repeated in all patients with HRPR, confirming the finding in all of them.

As shown in Table 1, patients with HRPR were more frequently diabetic ($p = 0.015$) and displayed higher levels of glycosylated hemoglobin and low-density lipoprotein (LDL) cholesterol ($p = 0.003$ and $p = 0.001$, respectively) and white blood cells ($p = 0.05$). No differences were observed in other demographic, clinical, or angiographic variables, but for a higher prevalence of severe multivessel coronary disease in patients with HRPR ($p = 0.03$). Mean platelet reactivity in HRPR patients was markedly enhanced in response to all activating stimuli ($p < 0.001$ for ASPI test, ADP test, COL test, and TRAP test).

As shown in Fig. 1, the prevalence of HRPR was stable in different high-risk subgroups of patients, such as in female gender (10.1% vs. 9.1%, $p = 0.99$) and patients with chronic kidney disease (0% vs. 10.7%, $p = 0.37$), whereas it was relevantly increased in diabetic patients (15.9% vs. 6.5%, $p = 0.045$), with a significant interaction between diabetic status and HRPR ($p = 0.04$).

However, at multivariate analysis, an impaired metabolic status, with higher levels of glycosylated hemoglobin and LDL cholesterol, but not diabetic status, emerged as independent predictors of HRPR with prasugrel [OR (95% CI) = 2.1 (1.32–3.33), $p = 0.002$ and OR (95% CI) = 1.03 (1.01–1.05), $p = 0.003$, respectively]. Complete data from the multivariable model are shown in Table 2.

Moreover, as displayed in Fig. 2, a stronger linear relationship was observed between ADP-mediated platelet aggregation and glycosylated hemoglobin levels ($r = 0.24$, $p = 0.002$, Fig. 2A), than for LDL cholesterol ($r = 0.13$, $p = 0.09$, Fig. 2B).

Discussion

The present study represents one of the largest cohorts of patients chronically treated with prasugrel, where the prevalence and predictors of suboptimal platelet inhibition on DAPT were

Table 1

Main clinical and demographic features in study population and according to platelet reactivity (HRPR) with prasugrel.

Clinical features	Overall	Prasugrel responders (n = 171)	Prasugrel HRPR (n = 19)	p-Value
Age (mean ± SD)	62.8 ± 9.2	63 ± 9.3	61 ± 8.4	0.37
BMI (mean ± SD)	28.2 ± 6.3	27.9 ± 6.4	30.3 ± 5	0.13
Male sex (%)	82.6	82.5	84.2	0.99
Hypertension (%)	72.6	72.5	73.7	0.99
Active smokers (%)	33.2	31.6	47.4	0.32
Diabetes mellitus (%)	30.5	27.5	57.9	0.015
Hypercholesterolemia (%)	55.8	55.6	57.9	0.99
Previous MI (%)	24.2	25.1	15.8	0.57
Previous PCI (%)	40	39.8	42.1	0.99
Previous CABG (%)	10.1	9.9	11.2	0.70
Renal failure (%)	7.9	8.8	0	0.37
ACS presentation (%)	61.4	61.8	57.9	0.95
ACE inhibitors (%)	54.5	57.1	31.6	0.05
ARBs (%)	21.7	20.6	31.6	0.26
Statins (%)	86.8	87.1	84.2	0.72
Beta blockers (%)	89.9	91.2	78.9	0.11
Nitrates (%)	42.9	42.9	41.1	0.99
Ca-antagonists (%)	28.6	26.5	47.4	0.07
Diuretics (%)	29.6	30.6	21.1	0.60
Ejection fraction (% ± SD)	53.4 ± 8.2	53.3 ± 8.1	54.5 ± 8.8	0.53
Left main/trivessel CAD	43.2	40.4	68.4	0.03
Main chemistry parameters				
Glycemia (mean ± SD)	117.7 ± 36.9	116.3 ± 36.5	131.2 ± 38.8	0.11
HbA1c (mean ± SD)	6.3 ± 1	6.2 ± 1	7 ± 1.2	0.003
Creatinine (mean ± SD)	0.91 ± 0.3	0.91 ± 0.3	0.88 ± 0.2	0.59
Cholesterol HDL (mean ± SD)	40 ± 10.3	40.3 ± 10.4	37.5 ± 8.5	0.29
Cholesterol LDL (mean ± SD)	74.6 ± 0.3	72.4 ± 22.9	94.6 ± 48.2	0.001
C-reactive protein (mg/dl, mean ± SD)	0.04 [0.13–0.42]	0.11 [0.04–0.37]	0.32 [0.05–0.72]	0.23
Platelets (10 ⁵ ml ⁻¹ ; mean ± SD)	246.1 ± 62	244.7 ± 62.7	258.6 ± 57.4	0.36
Hemoglobin (mean ± SD)	13.7 ± 1.9	13.7 ± 1.9	14.1 ± 1.2	0.30
WBC (10 ³ ml ⁻¹ ; mean ± SD)	7.8 ± 1.9	7.8 ± 1.9	8.6 ± 1.9	0.05
COL test (AUC; mean ± SD)	417.3 ± 160	395 ± 144.7	608.2 ± 160.8	<0.001
ASPI test (AUC; mean ± SD)	377.3 ± 187.7	353.5 ± 171	590.4 ± 200.2	<0.001
TRAP test (AUC; mean ± SD)	1143.3 ± 299	1112.6 ± 288.7	1490.9 ± 246.9	<0.001
ADP test (AUC; mean ± SD)	282.2 ± 152.5	243.9 ± 83.6	626.7 ± 193.5	<0.001

CAD, coronary artery disease; BMI, body mass index; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; STEMI, ST-elevation myocardial infarction; ACS, acute coronary syndrome; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blockers; LDL, low-density lipoprotein; HDL, high-density lipoprotein; WBC, white blood cells.

addressed. We identified HRPR with prasugrel in about 10% of patients and especially among patients with diabetes.

Recent advances in antiplatelet pharmacological therapies have allowed the optimization of antithrombotic strategies, thus reducing the rate of stent thrombosis and recurrent ischemic events and providing significant benefits in the outcomes, especially in the setting of ACS [20–22].

However, increasing complexity of current ACS patients is rendering more and more challenging the balance between

bleeding and thrombosis in the choice of DAPT strategies [23–25]. In fact, more advanced age and the higher rate of comorbidities, such as diabetes or renal failure, have dramatically raised the risk of bleeding complications, with negative consequences on the survival [26]. Nevertheless, these subsets of patients also display an enhanced pro-thrombotic status, with a baseline elevated platelet reactivity that has been previously associated with a suboptimal effectiveness of antiplatelet agents and recurrent ischemic events [27].

Previous studies, in fact, have documented the occurrence of HRPR in patients treated with DAPT, being associated with an increased rate of recurrent acute ischemic events and periprocedural thrombotic complications in patients treated with coronary stenting. In the recent collaborative analysis from different studies on the role of platelet reactivity for risk stratification after percutaneous coronary intervention, Aradi et al. [28] clearly

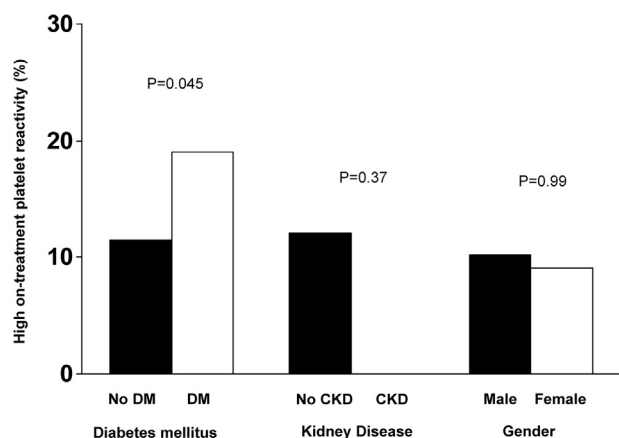


Fig. 1. Bar graph showing the prevalence of residual high-on treatment platelet reactivity in different subgroups of patients. DM, diabetes mellitus; CKD, chronic kidney disease.

Table 2

Results of the multivariate model for the identification of the predictors of high-platelet reactivity.

Variable	OR	95% CI	p-Value
HbA1c	2.1	1.32–3.33	0.002
LDL cholesterol	1.03	1.01–1.05	0.003
Diabetes mellitus	0.47	0.09–2.48	0.37
ACE-inhibitors	0.36	0.11–1.17	0.09
White blood cell count	1.18	0.89–1.56	0.26
Severe coronary artery disease	2.8	0.85–9.3	0.09

ACE, angiotensin-converting enzyme; LDL, low-density lipoprotein.

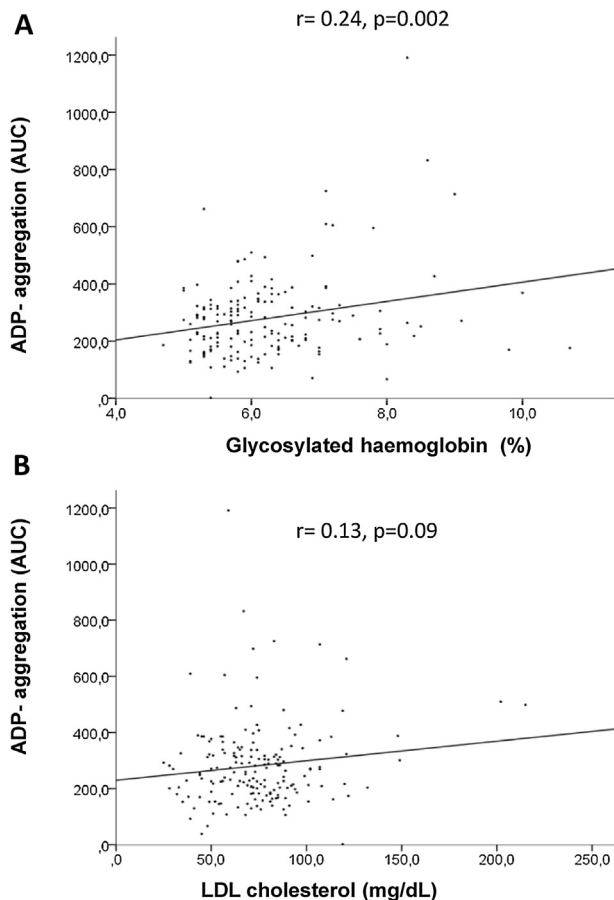


Fig. 2. Linear regression analysis displaying the relationship between area under the curve (AUC) at ADP multiplate test in prasugrel-treated patients and glycosylated hemoglobin (A, upper graph) and low-density lipoprotein cholesterol (LDL; B, lower graph).

showed in a cohort of over 20,000 patients undergoing PCI that HRPR had significantly higher risk for stent thrombosis [risk ratio (RR) and 95% CI: 2.73 (2.03–3.69), $p < 0.00001$], translating into increased mortality.

However, the majority of clinical data in these patients were obtained with clopidogrel, a pro-drug displaying a large inter-individual variability of effect, due to the several genetic and metabolic interactions with the processes leading to its activation [29].

The introduction of ADP-antagonists, such as prasugrel and ticagrelor, not requiring the same complex transformation as clopidogrel, has certainly provided a faster and more predictable platelet inhibition, thus translating into significant benefits in the prevention of recurrent ischemic events [30]. However, still suboptimal results have been achieved in higher thrombotic risk subsets of patients, such as diabetics, where we have recently reported a double rate of HRPR as compared to non-diabetic patients also with the more potent ticagrelor [31].

Among the ADP-antagonists, instead, prasugrel has demonstrated in the TRITON-TIMI 38 [32] a significant reduction in the rate of major adverse events in ACS patients undergoing invasive management, with even more positive results being achieved in diabetics rather than for subjects without diabetes (net clinical benefit with prasugrel 14.6% versus 19.2%; HR, 0.74; $p < 0.001$ in diabetics, 11.5% versus 12.3%; HR, 0.92; $p = 0.16$ in non-diabetics, p interaction = 0.05). An analogous conclusion, then, has been reached by Rossington et al. [33] in a meta-analysis of 4 randomized trials on diabetic patients with ACS, where prasugrel could

reduce the rate of recurrent myocardial infarction, without increasing the risk of major bleedings, especially among patients managed with PCI.

Contrasting with the clinical data of TRITON-TIMI 38, instead, Laine and colleagues [34] reported in 100 diabetic post-ACS patients that ticagrelor achieved a significantly lower platelet reactivity as compared to prasugrel loading dose. In addition, similar results have been achieved by Alexopoulos et al. in a cohort of 777 patients [35], thus raising potential concerns on the problem of suboptimal platelet inhibition also among prasugrel-treated patients, and especially in settings at higher thrombotic risk.

However, the magnitude of the problem of HRPR on prasugrel treatment is still largely undefined, with its rate varying among studies according to the methods and definitions applied [13,36].

The present study reports the data of 190 patients on a chronic maintenance therapy with prasugrel. We documented a rate of HRPR with prasugrel of 10% of the patients by the use of MEA.

In the SWAP-3 trial [37], among the 77 patients analyzed on prasugrel maintenance therapy, HRPR for prasugrel was 6.3% by light transmission aggregometry (LTA), a test that still represents the gold standard for assessing platelet function, with comparable levels of platelet inhibition being achieved by ticagrelor. Similarly, in the Optimizing anti-Platelet Therapy In diabetes Mellitus (OPTIMUS)-3 trial, that compared platelet reactivity with high-dose clopidogrel or prasugrel in a population of 35 diabetic patients, at 7 days, the poor responder rate ranged from 2.9% to 21.2% for prasugrel [38].

In a similar cohort of post-ACS patients, Siller-Matula et al. [39] documented HRPR with MEA aggregometry in 3% of the 107 subjects on prasugrel. However, their cohort included patients with younger age and lower rate of diabetes, hypertension, and other comorbidities as compared to our study, thus providing potential explanation for the difference in the prevalence of prasugrel poor-effectiveness. In fact, in a study by Cuisset et al., HRPR was much higher, occurring in about 8% of diabetic patients treated with prasugrel [40], thus not much dissimilar to the present results.

Moreover, in our study, we confirmed a higher rate of HRPR in diabetic patients, with a significant interaction between diabetic status and high platelet reactivity. However, at multivariate analysis only poor glycemic control, but not diabetes per se, emerged as an independent predictor of suboptimal platelet inhibition on prasugrel. Thus, it might be hypothesized that diabetic patients maintaining a good metabolic profile, could achieve a satisfactory platelet inhibition on prasugrel, therefore accounting for the positive results of this ADP-antagonist in the TRITON-TIMI 38 trial.

Indeed, Alexopoulos et al. [41] have previously documented in 233 patients that the independent predictors of HRPR on prasugrel were the levels of baseline platelet reactivity, ACS at presentation, and active smoking. In our cohort of patients, indication to DAPT was an acute cardiovascular event in almost the overall cohort of patients, and moreover, diabetic status and impaired glycemic control can certainly have conditioned an elevation of baseline pre-treatment platelet reactivity.

In fact, hyperglycemia can have an impact on platelet function directly and by modulating the release of pro-oxidant and inflammatory substances, inducing P-selectin expression and amplification of platelet adhesion [42]. However, the strict association between glucose control parameters and platelet reactivity has been well established only in patients treated with clopidogrel, where Singla et al. [43] have documented higher platelet aggregation on DAPT in patients with HbA1c levels above 7%. On the contrary, no data on the topic have been so far reported in prasugrel-treated patients, where the present study firstly documents that the effectiveness of this antiplatelet drug can also

be conditioned by glucose homeostasis. In effect, however, a similar conclusion had been suggested from the TRITON-TIMI 38 study, reporting larger benefits from prasugrel among diabetic patients treated with insulin (7.9% reduction in major adverse events vs. 4.8% in the overall diabetic cohort) [44].

Therefore, more aggressive antiplatelet strategies, together with a more rigorous control of other risk factors, such as glycemic status, can certainly provide the largest advantages in patients with acute cardiovascular events, and especially in higher risk settings such as in diabetics.

Nevertheless, whether tailoring antiplatelet treatment according to platelet reactivity will provide any significant improvement in the outcomes is still a matter of debate [45,46], and future randomized trials will certainly provide more conclusive indications for the management of these patients at higher thrombotic risk.

Limitations

A first limitation can be considered the relatively small sample size. However, as we aimed to describe the prevalence of a phenomenon in a real-world setting, where few data have been reported so far, we preferred not to perform a sample size estimation. However, our study represents one of the largest cohorts of patients where platelet function was assessed and moreover our conclusions were consistent with previous reports on the topic [38]. Indeed, the reduced number of patients in certain higher-risk subsets of patients, such as subjects with renal failure, and the greater statistical power for continuous variables, could potentially have affected the conclusions of our multivariable model, however the independent predictors of HRRP in our findings are in line with the data achieved in similar studies with other antiplatelet agents [43,47].

Another limitation can be considered the timing of platelet aggregation. The choice of evaluating patients on chronic antiplatelet therapy, after at least one month, was made on purpose, as Gurbel et al. [48] previously reported that the prevalence of HRRP on antiplatelet therapy progressively decreased within the first 30 days of treatment.

In addition, our results in patients with HRRP were not confirmed by using LTA, that still represents the gold standard for platelet aggregation. However, a good correlation between ADP-mediated impedance platelet aggregometry and ADP-LTA has already been reported [49].

In our study, elderly patients and subjects with low body weight, representing potential indications to the adjustment of prasugrel dose, were excluded, and therefore data on these categories cannot be provided from the present study, as we wanted to enroll a population receiving a standardized prasugrel dose of 10 mg.

Finally, we did not perform a systematic follow-up of our patients and therefore, we cannot definitely evaluate the impact of prasugrel non-responsiveness on clinical outcomes.

Conclusions

In post-ACS patients treated with PCI and receiving DAPT with prasugrel, HRRP is not infrequent, occurring in about 10% of patients. Impaired metabolic status, and especially elevated glycosylated hemoglobin, emerged as the only independent predictor of suboptimal effectiveness of prasugrel.

Authors' contribution

Monica Verdoia, MD: (1) Conception and design; (2) Data collection; (3) Interpretation of the data; (4) Drafting of the article; (5) Final approval of the manuscript.

Lucia Barbieri, MD, Matteo Nardin, MD: (1) Interpretation of the data; (2) Data Collection; (3) Critical revision of the article for important intellectual content of the article; (4) Final approval of the manuscript.

Roberta Rolla, MD, Paolo Marino, MD: (1) Interpretation of the data; (2) Critical revision of the article for important intellectual content of the article; (3) Final approval of the manuscript.

Giorgio Bellomo, MD, Patrizia Pergolini, MD: (1) Interpretation of the data; (2) Critical revision of the article for important intellectual content of the article; (3) Evaluation of platelet reactivity; (4) Final approval of the manuscript.

Giuseppe De Luca, MD, PhD, Hatty Suryapranata, MD, PhD: (1) Conception and design; (2) Statistical analysis; (3) Interpretation of the data; (4) Drafting of the article; (5) Final approval of the manuscript; (6) Supervision.

Conflict of interest

The authors declare no funding source or conflict of interest to disclose.

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